

# Nickel-Catalyzed Reductive Coupling of Unactivated Alkyl Bromides and Aliphatic Aldehydes

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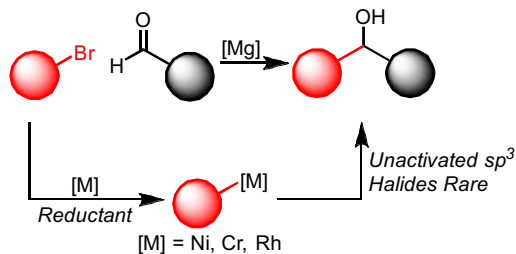
**ABSTRACT:** We report the development of a mild, convenient coupling of aliphatic aldehydes and unactivated alkyl bromides. The catalytic system features the use of a common Ni(II) precatalyst and a readily available bisoxazoline ligand and affords silyl-protected secondary alcohols. The reaction is operationally simple, utilizing Mn as a stoichiometric reductant, and tolerates a wide range of functional groups. Initial mechanistic experiments support a mechanism featuring an alpha-silyloxy Ni species which undergoes formal oxidative addition of the alkyl bromide species via a reductive cross-coupling pathway.

The coupling of carbonyl compounds and carbon-nucleophiles is of broad interest to the chemical community to build molecular complexity. The most ubiquitous methods are perhaps the Grignard and related Barbier-type reactions that transform organohalide coupling partners into suitable organometallic nucleophiles. However, the need to pre-generate highly reactive organometallic intermediates is undesirable from a functional group compatibility standpoint, and is occasionally non-trivial, especially on small scales relevant for high-throughput experimentation.<sup>1-3</sup> While Barbier-type conditions allow for *in-situ* generation of organometallic nucleophiles, these are generally restricted to activated allylic or propargylic halides.

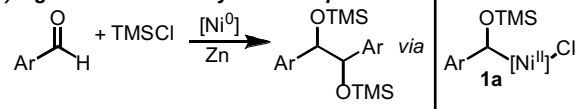
An especially appealing strategy for introducing Grignard-type couplings to medicinal chemistry efforts is through transition-metal catalysis. These processes are attractive due to the generation of milder nucleophilic partners and higher control of selectivity by tuning the catalytic system and have been employed on process scales.<sup>4-6</sup> Net reductive couplings using organohalide feedstocks have been developed using stoichiometric reductants to achieve catalytic activity, obviating the need for pre-generation of the organometallic nucleophile.<sup>7-13</sup> Among the most common systems are Rh<sup>7</sup>, Ni<sup>8,11,14,15</sup> and Cr<sup>16-21</sup>-catalyzed couplings of aldehydes and organohalides. Importantly, each of these systems are proposed to proceed via Grignard-type mechanisms, generating organometallic nucleophiles that undergo formal additions to carbonyl electrophiles.<sup>8,11,17,22</sup> The vast majority of Ni-catalyzed couplings of this type only tolerate aromatic aldehydes and either aryl, allylic or propargylic halides.<sup>8,10,12,13,15,23,24</sup>

## Scheme 1. Strategies for Forging C-C Bonds from Aldehydes and Halides.

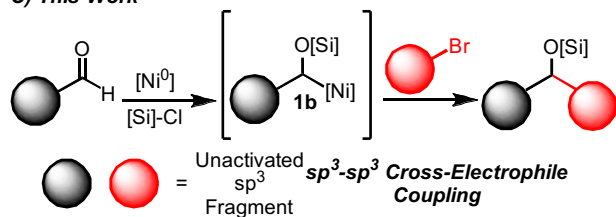
### A) Grignard and Transition-Metal Catalyzed Barbier Couplings



### B) Ogoshi - Masked Acyl Anion Equivalents



### C) This Work

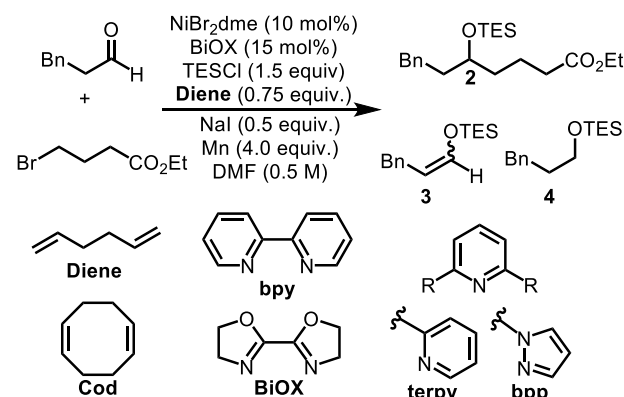


The limitations of existing methods are potentially derived from the involvement of the metalated nucleophilic intermediates involved in these transformations.<sup>8,11,22</sup> Aliphatic aldehydes are less suitable coupling partners for the organonickel intermediates generated from oxidative addition of aryl halides, as noted by Weix<sup>8</sup>. Additionally, controlling the selective activation and heterocoupling of alkyl halides under reductive conditions is a considerable challenge as homocoupling pathways are often favorable.<sup>25-27</sup>

Due to these challenges a significant gap remains in the development of reductive couplings of aldehydes and alkyl fragments, especially for combinations of aliphatic aldehydes and unactivated  $sp^3$  fragments. Cr-catalyzed couplings of alkyl halides (using Co co-catalysis) have been

demonstrated; however, examples are limited.<sup>28a</sup> Alternative coupling partners such as redox-active esters have offered access to similar skeleton frameworks, although similar issues of homocoupling can be encountered.<sup>9,10</sup> An electrochemical Cr-catalyzed coupling of redox-active esters and aldehydes has been recently demonstrated by Reisman, Blackmond, and Baran.<sup>28b</sup> While the scope of the electrochemical process is exceptionally broad, examples with aliphatic halides and aliphatic aldehydes were not illustrated. Key developments from MacMillan similarly provide a broad array of substrate combinations in additions of various bromides to aldehydes through a method that involves acyl radical additions.<sup>29</sup> This method illustrates rare examples of introducing sp<sup>3</sup> alkyl fragments from alkyl bromides to provide products in the ketone oxidation state. Additionally, various feedstocks have been used for the synthesis of ketones in related nickel-catalyzed or NHC-catalyzed processes.<sup>30–32</sup> Other selective couplings of alkyl organonickel nucleophiles derived from alkyl halides have been described by Martin, and their use has been focused thus far to trapping with electrophiles such as CO<sub>2</sub> and isocyanates.<sup>33–36</sup>

**Table 1. Optimization of Reaction Parameters.<sup>a</sup>**



Entry	Deviation	2 (%) <sup>b</sup>	3 (%) <sup>b</sup>	4 (%) <sup>b</sup>
1	none	93	<5	<5
2	no NaI	76	10	10
3	no diene	46	20	20
4	1-octene instead of diene	76	10	12
5	Cod instead of diene	59	19	23
6	bpy instead of BiOX	15	24	21
7	terpy instead of BiOX	0	40	30
8	bpp instead of BiOX	47	27	20
9	PPh <sub>3</sub> instead of BiOX	0	50	50
10	Zn instead of Mn	85	ND	0
11	TMSCI instead of TESCI	46	ND	ND
12	No Ni	0	<5	0
13	No Ligand	0	10	0
14	No Mn	0	10	0

ND = Not Determined a) Unless otherwise stated, reactions were run on a 0.2 mmol scale with respect to the aldehyde substrate and 2.0 equiv. of alkyl bromide. b) Yields were determined either by NMR vs. mesitylene or by GC-FID with 1,3,5-trimethoxybenzene as an internal standard.

In order to circumvent these challenges in reductive aldehyde / alkyl halide couplings we envisioned developing a method to activate aldehydes as acyl anion equivalents.<sup>37–40</sup> A key report from Ogoshi detailing the formation of alpha-silyloxy Ni(II) complexes of type **1a** (**Scheme 1B**) from

Ni(0) sources, aldehydes and silyl chlorides provided inspiration towards this goal.<sup>41</sup> Indeed, Mackenzie<sup>42</sup> and Weix<sup>8,43</sup> have shown that similar allyl complexes derived from Ni(0), Michael acceptors and silyl chlorides undergo C-C coupling with appropriate organohalide sources. We hypothesized that the generation of this  $\alpha$ -silyloxy Ni-complex **1b** (**Scheme 1C**) could be leveraged with known Ni-catalyzed cross-electrophile coupling reactions of unactivated sp<sup>3</sup> halides to afford silyl-protected ether products.<sup>27</sup>

An initial screen of ligands commonly employed in reductive cross-couplings revealed BiOX as a uniquely promising candidate for selective coupling (see SI for more optimization details). In all reactions, competitive formation of the corresponding enol ether **3** and reduced silyl ether **4** in addition to homocoupling of the alkyl bromide was observed. Upon further screening we found that olefin additives could minimize the formation of these side products, while affording better mass balance and higher yields, with excellent reactivity observed when using 1,5-hexadiene. Further optimization revealed that when using 75 mol% of this additive, in addition to 50 mol% of NaI, excellent yields of the desired cross-coupled product were obtained.

With optimized conditions in hand, we explored the scope of the reaction. Varying the aldehyde component revealed that the reaction tolerated a number of steric environments around the aldehyde coupling partner as well as chemoselective activation of the aldehyde (**Scheme 2**). Benzyl ethers and straight-chain aldehydes were shown to couple effectively. Substrates with  $\beta$ -branching, such as citronellal (**7**) and isovaleraldehyde (**8**), delivered the desired products in good yield. Aldehydes bearing protected amines such as carbamates were well tolerated, showing no activation or cleavage of the Boc group in **9**.  $\alpha$ -Branched aldehydes showed comparable reactivity to linear substrates (**10–13**), however, aldehydes bearing  $\alpha$ -quaternary centers did not afford meaningful amounts of coupled product.

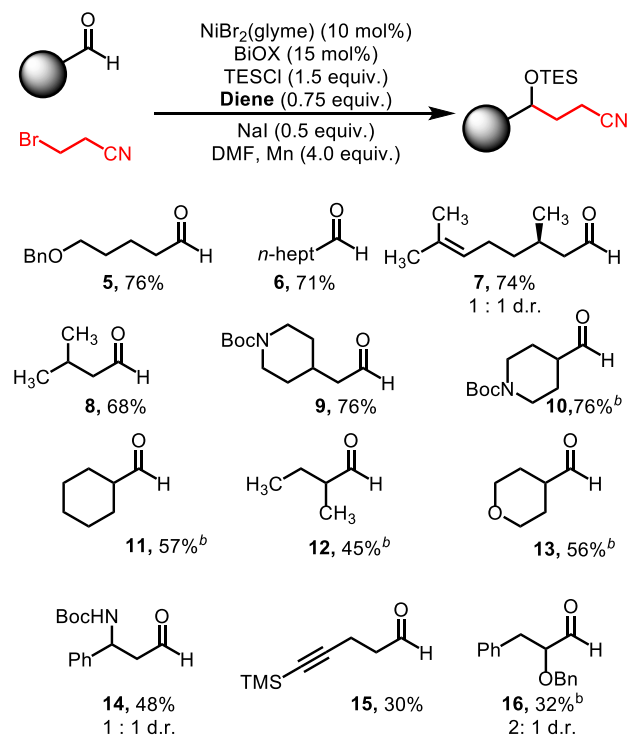
Alkyne functionality was also tolerated, affording modest yields of the carbonyl coupling. Additionally, decreased reactivity was observed when heteroatom functionality is located at the  $\alpha$ -position (**16**). The reaction displayed good reactivity for aldehydes, however ketones afforded minimal amounts of coupled products. Additionally, aryl aldehydes are incompatible with this coupling and afford no desired product at the expense of undesired pinacol coupling (see SI for details).<sup>41</sup>

Exploration of the scope of the alkyl bromide coupling partner displayed similarly broad functional group compatibility (**Scheme 3**). As a general note, while we found that the inclusion of NaI was beneficial during the initial optimization with ethyl 4-bromobutyrate this benefit was not always observed. In some cases, the inclusion of NaI led to decreased yields of the desired products. We attribute this to enhanced reactivity of certain alkyl iodide substrates generated from in-situ HalEx reactions (see SI for more discussion).

Esters, nitriles, and phosphonate ester functionality (**2,17–19**) is well tolerated and afford high yields of coupled products, highlighting the mild nature of these conditions. Alkyl and aryl-chlorides (**20, 22**) are not activated under these conditions, nor are boronate esters (**23**), offering

further sites for derivatization via other cross-coupling systems. Ethers (**24**) and acetates (**25**) are coupled in excellent yields, allowing for polyol structures to be constructed.

### Scheme 2. Aldehyde Reaction Scope.<sup>a</sup>



a) General reaction conditions on a 0.5 mmol scale: Aldehyde (1.0 equiv.), 3-bromopropionitrile (2.0 equiv.),  $\text{NiBr}_2(\text{glyme})$  (10 mol%),  $\text{BiOX}$  (15 mol%),  $\text{TESCl}$  (1.5 equiv.), **Diene** (0.75 equiv.),  $\text{NaI}$  (0.5 equiv.), Mn (4.0 equiv.), DMF (1.0 mL). Yields refer to isolated yields; b) Reaction run without NaI.

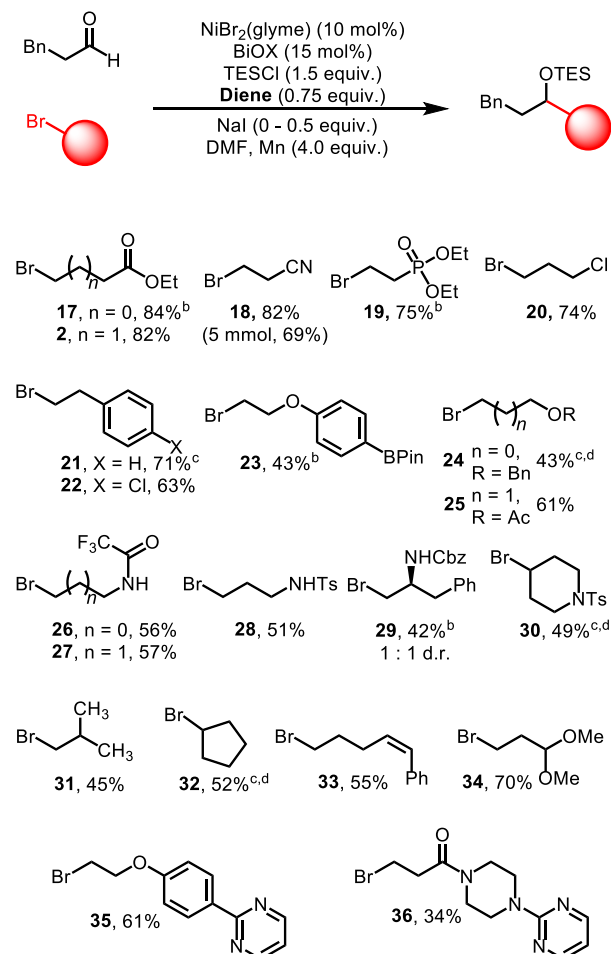
Protected amine functional groups, such as trifluoroacetamides (**26-27**), sulfonamides (**28**) and carbamates (**29**) are also tolerated. Sterically encumbered bromides such as protected piperidine derivatives (**30**), isobutyl bromide (**31**) and cycloalkyl bromides (**32**) are competent coupling partners, albeit displaying diminished yields. Secondary bromides such as **30** and **32** could be coupled in moderate yields when LiBr is used in place of NaI.<sup>44</sup>

We also found that more activated olefins are not susceptible to competitive reactions under these conditions as evidenced by the clean coupling of substrate **33**. Additionally, the geometric configuration of the olefin is maintained throughout the reaction, suggesting that  $\beta$ -hydride elimination or chain-walking processes related to activation of the bromide are slow in this catalytic system. Potentially Lewis acidic sensitive groups such as acetals (**34**) are also tolerated. Finally, heterocyclic functionality is tolerated, as evidenced by the clean participation of pyrimidine structures **35** and **36**. Efficient coupling was also demonstrated on a 5.0 mmol scale, obtaining coupled product **18** in slightly diminished yield (69%).

We anticipated that the features of the reaction observed during our initial optimization, particularly the formation of enol ether **3** and silyl ether **4** (**Table 1**) may shed light on key intermediates in the catalytic pathway. Stoichiometric experiments revealed similar product distributions observed under the catalytic conditions. When using  $\text{Ni}(\text{cod})_2$

and equivalent amounts of aldehyde and bromide, a 27% yield of the coupled product **2** was observed (**Scheme 4A**). In addition, undesired products **3** and **37** were also observed in 8% and 21% yield, respectively. Additionally, when  $\alpha$ -oxy aldehyde **16** was subjected to a stoichiometric reaction, enol ether **3** was observed in 52% yield in addition to 50% yield of silyl ether **40**. The formation of both of these species would be consistent with a sequence outlined in **Scheme 4A** wherein intermediate **40** undergoes  $\beta$ -oxy elimination to furnish **3**, and the resulting nickel alkoxide **40** undergoes silylation with TESCl to furnish **38**.

### Scheme 3. Bromide Reaction Scope.<sup>a</sup>



a) General reaction conditions on a 0.5 mmol scale: Dihydrocinnamaldehyde (1.0 equiv.), Alkyl Bromide (1.0 - 2.0 equiv.),  $\text{NiBr}_2(\text{glyme})$  (10 mol%),  $\text{BiOX}$  (15 mol%),  $\text{TESCl}$  (1.5 equiv.), **Diene** (0.75 equiv.),  $\text{NaI}$  (0.5 equiv.), Mn (4.0 equiv.), DMF (1.0 mL). Yields refer to isolated yields; b) Reaction run without NaI; c) Reaction run with 1.0 equiv. LiBr instead of NaI; d) Product isolated as the corresponding alcohol following TBAF deprotection.

The observation of **3** and **37** in both the stoichiometric experiments as well as the catalytic coupling conditions suggest a common mechanism for their formation. Control experiments confirmed that the aldehyde is only consumed when both Ni(II) salt and reductant are present (see SI for details). This observation is consistent with activation of the aldehyde via interaction with a low-valent Ni species. Additionally, when the silyl chloride is omitted, complete consumption of the aldehyde is observed to give a complex

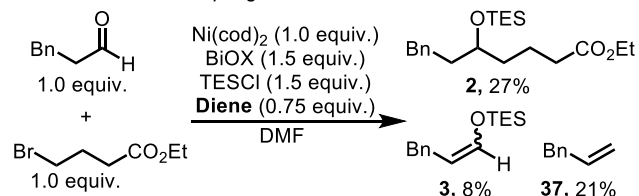
mixture, suggesting that the presence of silyl chloride leads to stabilization of a key intermediate leading to formation of the coupled product. Importantly, only trace enolization is observed when Ni is omitted from these reactions, ruling out a background silyl-mediated enolization as a pathway to generate HCl, which could react to form a nickel hydride species.

Taken together, these results provide preliminary evidence for the formation of an  $\alpha$ -silyloxy Ni species under the reaction conditions. A catalytic cycle combining these

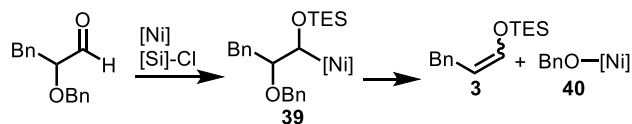
### Scheme 4. Mechanistic Considerations and Catalytic Cycle.

#### A) Stoichiometric Experiments

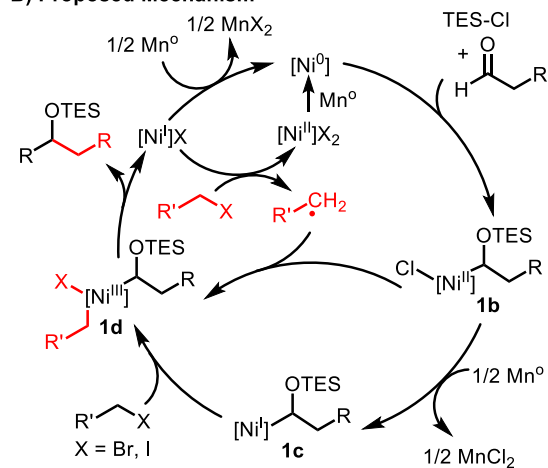
##### Stoichiometric Ni Coupling



##### -Deoxygenation

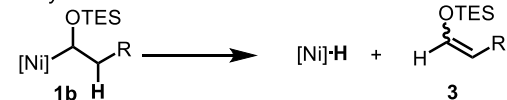


#### B) Proposed Mechanism

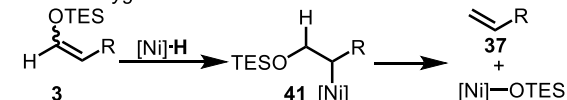


#### C) Pathways for Side-Product Formation

##### -Hydride Elimination



##### Ni-H Deoxygenation



observations is shown in **Scheme 4B**. First, following reduction of the Ni(II) pre-catalyst, Ni(0) undergoes complexation with the aldehyde substrate and TESCl to furnish intermediate **1b**. This intermediate can then engage the alkyl halide coupling partner either via a radical-chain process as noted by Weix<sup>27</sup> or through a sequential reduction – oxidative addition pathway<sup>45</sup>. Regardless of the exact nature of this step, the resulting dialkyl Ni(III) intermediate can then undergo reductive elimination to furnish the coupled product and a Ni(I) salt. This Ni(I) salt can then either undergo reduction by Mn to regenerate the active Ni(0) catalyst or activate another equivalent of alkyl halide to further the radical chain process. A stoichiometric reaction between aldehyde and alkyl bromide, in the absence of TESCl, afforded only bromide dimer and did not form any cross-coupled alcohol product. This result is inconsistent with an alternative mechanism wherein an alkyl-Ni nucleophile forms and undergoes a formal migratory insertion with the aldehyde substrate to forge the C-C bond.<sup>33</sup>

The formation of **3** and **4** can be explained via undesired side-pathways of silyloxy intermediates **1b** or **1c** (**Scheme 4C**). Beta-hydride elimination from any silyloxy-Ni intermediates would result in the formation of derivatives of **3** and a Ni-H species. Reinsertion of this Ni-H species into **3** can afford a new alkyl-Ni intermediate **41** poised to undergo  $\beta$ -oxy elimination to furnish allylbenzene **37** and a Ni-alkoxide. Furthermore, the Ni-H generated via beta-hydride elimination can alternatively reduce an equivalent of aldehyde which would lead to **4** observed in reaction mixtures. The role of 1,5-hexadiene in minimizing the formation of these side-products may play a role in suppressing the formation of Ni-H, acts as a sacrificial hydride acceptor, or simply stabilize the low-valent nickel intermediates involved.<sup>46,47</sup> Further studies are underway to better understand the role of this additive.

In conclusion, an efficient reductive coupling of aliphatic aldehydes and unactivated alkyl halides has been developed. The process addresses a key limitation of prior methods, specifically the ability to introduce unactivated C(sp<sup>3</sup>) groups in both the aldehyde and alkyl halide reaction components. Additionally, the process tolerates a wide range of functionality and is amenable to larger scale syntheses. The reaction utilizes an air-stable Ni(II) pre-catalyst and easily synthesized BiOX ligand. Preliminary mechanistic experiments suggest a novel mechanism proceeding through a silyloxy-Ni intermediate that effectively engages a free radical derived from an alkyl halide. Efforts to expand the scope of coupling partners and devise more efficient catalytic systems are currently underway.

## ASSOCIATED CONTENT

**Supporting Information.** Optimization tables, experimental data, copies of spectra. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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